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title page

Special treatment? Flexibilities in the politics of regenerative medicine's gatekeeping regimes in the UK

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Abstract

Emerging flexibilities are apparent in gatekeeping regimes applicable to regenerative medicine products, raising issues about the extent to which and forms in which such flexibilities might promote emerging products as a sector warranting special treatment, in the context of recent policy developments in the UK and wider European Union. Concepts of 'gatekeeping', 'gatekeeping regimes' and 'gateways' can point to the ways in which regulatory institutions, health technology assessment organisations, and national planners and purchasers of health services together define and control entry to the medical product marketplace and the adoption of products into the public healthcare system. Flexibilities in existing regimes and new gateways are a way of maintaining 'connection' between gatekeeping regimes and technoscientific innovation in order to steer innovation pathways. The gateways concept has affinity with that of Callon's 'obligatory passage points'. A wide set of recent policy documents show that the measures promoted exhibit a range of alternative gateways that are being constructed around central, legal, restrictive gatekeeping regimes. However, it would be easy to over-estimate the significance of these developments as relaxations that would favour innovative producers and their products on a large scale with wide public health impacts. The concepts of gatekeeping regimes and gateways enable understanding of hybrid developments of exceptions and exemptions to dominant regimes which bridge across the arenas of market regulation, health technology assessment and healthcare system planning. These arenas are being drawn closer together as a means of politically managing stakeholders' aims in the UK, EU and other innovating biomedical health systems globally.

Keywords

Regenerative medicine; gatekeeping; regulation; policy; advanced therapy medicinal products; United Kingdom; flexibility

Introduction

The global field of cell-based and tissue-engineered regenerative medicine is diversifying, as a wide range of biological mechanisms and therapeutic delivery technologies are developed, tested, trialled and, occasionally, introduced into clinical practice. The field is the subject of enormous expectation of its eventual promise to revolutionise many areas of medical therapy, including cancer, diabetes, arthritic disease, heart conditions and neurodegenerative diseases. It is in effect a nascent sector which many see as deserving special treatment through incentives and regulatory concessions in order to promote it. The technical novelty, evidential uncertainty and high promise of technologies in the field exacerbate the normal tensions of combining facilitation of innovation and limitation and control in medicines regulation (Kennedy, 1978; Faulkner and Kent, 2001). Regulation can be both enabling and restrictive of scientific innovation and product development, and this tension has been exacerbated in the health sector due to the rise of 'risk regulation' following various public

health safety disasters such as BSE (Vogel, 2001). Different countries have tackled the regulation of these sciences, materials and technologies in widely different ways, resulting in a segmented marketplace of different regulatory regimes involved in constituting globally the emerging practices and products of the new regenerative medicine paradigm.

An important force shaping the regenerative as well as conventional medicines innovation field is the international ('Western') policy response to the global slowdown in regulatory approval of new pharmaceutical therapies. The US Food and Drug Administration (FDA) has introduced a 'fast track designation' and more recently its 'breakthrough therapy designation' for drugs able to demonstrate a substantial improvement over existing therapies. Both FDA and the European equivalent, the European Medicines Agency are linked partly to the 'New Drugs Paradigms' (NEWDIGs) international initiative, started in 2010 as a forum for co-ordinating and exploring the movement from the dominant binary yes/no boundary-keeping decisions on the market authorisation of drugs to a more flexible, stratified approach. Moderated by the MIT Center for Biomedical Innovation, the NEWDIGs initiative also involves the UK's national regulator the Medicines and Healthcare products Regulatory Agency (MHRA), Health Canada, the Singapore Health Services Authority as well as sponsors, health technology assessment organizations, reimbursers/payers, patient associations and academics. The initiative is aimed 'on enhancing the capacity of the global biomedical innovation system to reliably and sustainably deliver new, better, affordable therapeutics to the right patients faster' (NEWDIGs, 2016), a ringing endorsement of current political 'innovation' agendas. The field is also shaped by massive policy actions such as the Innovative Medicines Initiative (IMI) which is Europe's largest public-private enterprise, aimed at accelerating the development of safer and improved medicines. IMI is a joint undertaking between the European Union and the pharmaceutical industry association EFPIA and supports collaborative research projects and networks across industry and academia (<http://www.imi.europa.eu/>), funded at £3.3 billion in the period 2014-24. There is thus broad pressure globally to reform medicines innovation processes and regulation. This pressure is also apparent in the development of the regenerative medicine field.

In the United Kingdom, the last few years have seen a major set of policy initiatives and actions to boost the UK's regenerative medicine activity for both 'health' and 'wealth' objectives. These initiatives include a 2011 government 'Life Sciences Strategy' and a 2013 House of Lords report on Regenerative Medicine (HoL, 2013) which proposed a wide range of investments and infrastructural developments specifically to promote regenerative medicine as a sector in which the UK would excel on the world stage. The UK's legal regulatory activity in the field of regenerative medicine has been conditioned by its position in the European Union and especially, though not exclusively, the Advanced Therapy Medicinal Products Regulation of 2007; its (England's) public healthcare adoption activity is undertaken notably by technology assessment-based policy body NICE (National Institute for Health and Care Excellence) and commissioning/service contractor NHS England. Both arenas are the site of a range of contests about

whether, and if so, how, regenerative medical technologies might be accorded special treatment as a sector. A range of sometimes opposing forces of restrictive and pro-innovation politics applies both to the arenas of legal regulation of market entry and to the regulation of healthcare commodities' adoption through processes of technology assessment and healthcare payers, which in the UK are called 'commissioning' agencies, who develop contracts with providers such as hospitals for the delivery of packages of healthcare to the population. This paper analyses developments in each of these two constituencies, the market/practice entry regulators on the one hand and the healthcare system assessment and adoption agencies on the other, in order to pose the questions: to what extent is there flexibility in or alongside the existing and emerging dominant central market entry and assessment/adoption regimes, what forms do they take, and to what extent do such flexibilities promote the emerging regenerative medicine sector?

Conceptualising regenerative medicine gatekeeping in the UK

Elsewhere, I have written about the roles of the political negotiation of regulatory categories of different medical products as an important dynamic constituting the innovation environment of new medical technologies (Zhao, 2005; Faulkner 2009a, 2012c). Conspicuous amongst these is the issue of how legal concepts and regulatory institutions can be 'matched' to the scientific, technological and industrial categories that emerge, or which are produced, in the development and testing of complex new medical materials, and how these vary in the framings of different, bounded legal regimes such as national political cultures, building on existing regimes. This key issue has usefully been termed 'regulatory connection' (Brownsword, 2008). While laws and regulations are developed as polities and societies try to maintain regulatory connection, various forms of institutional gatekeepers wrestle with the technoscientific and stakeholder issues that arise at the interface between innovative practices and regulatory concerns.

This paper develops the concepts of 'gatekeeping', 'gatekeeping regimes' and 'gateways' as a general way of combining the assessment for, and policing of, on the one hand the market entry and on the other hand the healthcare uptake of new cellular medical products. I adopt these concepts in preference to 'regulation', mostly interpreted to refer to formal statutory law-based gatekeeping, standard-setting and guidance, and to 'governance', generally taken to refer to looser, network-based, partly distributed forms of societal shaping of innovation (Rhodes, 1997). Control over the marshalling and flow of information has long been recognised in the sociology of organisational power as a key resource that 'gatekeepers' seek to deploy (Pettigrew, 1972). Gatekeeping also, more than those related concepts, draws attention to the policing of the boundaries of entry of products or services into adoption processes, usership practices and the marketplace, and a potential range, to extend the territorial boundary metaphor, of 'gateways' through which actors and technologies might pass.

The family of concepts of gatekeeping using this terminology *per se* has not been greatly elaborated in social science studies of risk-related medical (or other sector) innovation. I start to develop it in this discussion, therefore, in accordance with both common-sense usage and noting its status as part of the normal vocabulary of leading international regulatory voices in the medical field (Ehman et al, 2013: 'regulators are expanding their role to be not only *gatekeepers* but also enablers of development' (Abstract, my emphasis). The notion of regulatory regime (e.g. Scott, 2004), as an institutionalised set of rules, practices, expertise and actors accorded special authority in a given sector of society, has become widely used, and is connected to the theorisation of the 'regulatory state' (Moran, 2001), where command-and-control government is seen to be shifting toward more diffuse modes of governance in which multiple agencies participate in policymaking and implementation, at least in democratic polities. The concept of regulatory regime has been used for example in studies of the food sector (Buonanno et al, 2001), telecommunications (Bollhoff, 2002) and education (Baxter, 2013). I therefore adapt this concept to understand 'gatekeeping regimes' more specifically as sets of rules, practices, knowledges and institutions focally concerned with patrolling the boundaries of the emerging regenerative medicine marketplace and adoption in healthcare systems through rules of entry. Gatekeeping, therefore, as I use the term here, has a role in shaping both technological innovation itself, as well as the innovation pathways that technology developers are able to take in attempting to bring products into the marketplace and into healthcare practice. Gatekeepers create and work through what can be conceived as gateways to shape emerging technological zones or fields, their industrial and scientific actors, emerging markets, their clinical and citizen usership, and their rules of engagement (Faulkner, 2009a, 2009b, 2012a). Like regulatory connection, 'gatekeeping connection' can thus be conceived of as processes by which gatekeepers and gateways adjust in order to maintain purchase on the shifting, unstable dynamics of an innovative technoscientific field.

Adopting the concepts of gatekeeping and gateways, Callon's well known concept of the obligatory passage point (Callon, 1986) is useful to refer to here. The marine biologists in Callon's well known account of scallop fishing in France sought to make themselves into inescapable orchestrators of a campaign by defining the technoscientific problem that other actors would have to agree to in order to advance their cause in the case at hand (in this case, 'how do scallops anchor?' p8), a process that Callon called problematisation. This problem-defining move can also be aligned with the situation-defining concept of agenda-setting (cf. van Merkerk et al, 2006) in an emerging technoscientific field. Although Callon's seminal notion revolved around what was in essence a multi-stakeholder *project*, I propose that it can also be applied to sociotechnical institutions that have achieved the status of the authority to perform gatekeeping functions and to define gateways that have become unavoidable for groups of actors or would-be actors in a given field. In the case of the gatekeeping constituencies to be considered here, authoritative structures are already in existence and given societal legitimation, contested though that status may be. Thus the

ability of these actors to assert problem definitions and obtain acquiescence to the rules of the game, is less precarious than in Callon's case, and has become structural and historically embedded in a way that cannot be ignored by would-be participants. The gatekeepers that I discuss here are thus able to define the problems and maintain their gatekeeping functions, even though as will be shown, they adapt and innovate their own rules and methodologies in doing so, thereby mandating a range of more and less formal alternative gateways for innovative actors and technologies. In other words, although the gatekeepers' projects can be described as regulatory standardisation in action, this standardising mission encounters some powerful and persuasive, and to some extent effective, modification and opposition.

The last decade has seen the development in Europe of a number of regulatory policy initiatives, including some novel gateways for biomedical innovation, that can be seen as relaxations by centralised, mandated EU-wide or national gatekeeping actors, under specific conditions, of the basic regulatory frameworks, infrastructures, data requirements and dominant technology assessment gatekeeping regimes. This trend appears to be increasing as different regimes and their gatekeepers struggle with the dilemmas of innovation and potential health benefit that regenerative medicine and its proponents raise. This leads us to ask: In what sense might regenerative medicine or cell therapy be framed and constructed in market regulation and healthcare system innovation as a special sector or zone deserving of its own gatekeeping conventions, its own gateways to markets and health system/clinical adoption, and support systems? How do regenerative therapy movements counter and influence the systemic standardisation embedded in existing, 'inherited' (Stokes, 2012) regulatory regimes?

To address the question of the extent, forms and significance of flexibility in dominant gatekeeping regimes, the paper analyses recent and current regulatory and gatekeeping strains of policy discourse and activity, primarily in the UK and European context. I analyse these trends in terms of the tension between commensuration with inherited classificatory domains and technoscientific standards on the one hand (Faulkner, 2012b), set against counter-movements of exceptionalism and exemptionalism on the other. I show that there is a trend in gatekeeping regimes to create flexibility and alternative gateways to the rules of entry to the regenerative medicine marketplace and healthcare systems through various exemptions, exceptions and conditional alternative gateways to established paradigms, noting that this flexibility varies across different jurisdictions. But I argue that, although indeed the overall effect is one of somewhat hybrid, diversifying, imbalanced frameworks, it would be easy to overestimate the extent of these developments. In concluding I point to reasons why this is so, and consider the extent to which these developments that temper 'obligatory' centralised, dominant passage points are able to maintain gatekeeping connection and adoption pathways for regenerative medicine innovations. Table 1 summarises the range of developments that I discuss in the paper, differentiating conceptually between on the one hand legal, regulatory gatekeeping of market entry, and on the other hand alternative and

conditional gateways to healthcare adoption, with a category of hybrid, overlapping, conditional gateways in between.

The structure of the paper is as follows. Following a brief description of data sources, I tackle first the gatekeeping regimes around entry of products into the marketplace and usership (Faulkner, 2009b), and then move on to consider the specific case of exceptionalism in the UK's national methodologies and institutional practices in evaluating, guiding, and adopting regenerative medical technologies, in the context of the national healthcare system (NHS), which remain under debate at the time of writing (Autumn 2016). I then discuss current moves to bridge the gap between market entry gatekeeping and healthcare system adoption gatekeeping, and conclude by commenting on the significance of the trends surveyed and on the applicability of the conceptual apparatus elaborated in the paper.

Method

The paper draws on former and current ESRC supported research projects, which had university research ethics committee approval. These involved extensive document collection, interviewing by research teams of a wide range of stakeholders, and attendance at policy related meetings from 2013 to 2015. The discussion here refers primarily to a range of data sources in the form of published documents, regulations, laws, policy statements, expert commentaries and the like, which are in the public domain. It should be noted that exact product and company names often cannot be presented, because this information is confidential to the gatekeepers in question primarily for commercial reasons.

Gatekeeping the marketplace

Gatekeeping of entry of medical products to the EU (and thus in principle the UK) marketplace rests primarily on pharmaceutical and Advanced Therapy Medicinal Product (ATMP) law, operational since 2001 and 2007-8 respectively. Here I discuss the exceptions and exemptions, the alternative gateways, that have been introduced with the gatekeeping regime comprising relevant Directives and Regulations (which I do not detail legalistically here), and related measures. Substantively, the key gatekeepers, representing the dominant gatekeeping regime are the central European Medicines Agency, and since 2007 (see below) the Committee for Advanced Therapies, a specialist committee dealing with regenerative products of various types (see below, and Table 1). These institutions assemble multidisciplinary scientific expertise to evaluate products presented to them by manufacturers, to classify them, and to make decisions about market authorisation based on detailed preclinical and clinical data dossiers. A small number of products have been classed as 'ATMPs' over the last decade, including for example Holoclar® the first such product to contain stem cells, indicated for treating moderate to severe limbal stem cell deficiency (LSCD) due to physical or chemical burns to the eye in adults, and ChondroSelect®, the first ATMP approved centrally in Europe, a 'tissue-engineered' cell-based product indicated for repair of symptomatic cartilage defects of

the knee joint. In the UK, the equivalent tasks of assessment and policing are undertaken by the Medicines and Healthcare products Regulatory Agency (MHRA) which also inspects manufacturing premises and assesses the expertise of production managers ('Qualified Persons' (QPs)) at medical products manufacturing sites. At the time of writing no UK-originated regenerative products have been approved as ATMPs through the centralised EU process.

In the EU, applicable to pharmaceutical products and thus in principle regenerative medicines, three main 'licensing flexibilities' intended to improve developers' incentives have already been introduced. First, one such regulation-relaxing development that has emerged for products designated as medicines is the *conditional approval* – essentially a leap-frogging of Phase 3 studies (scaled-up studies in patients) and launching of a Phase 4 study (final phase of study required) once a product has been marketed. Proponents argue that this might speed up bench to bedside translation by approving technologies with less than complete safety and efficacy data. However, one analysis suggests that approval times are not necessarily shortened (Boon et al, 2010). The procedure is applicable when there is a complete pharmaceutical and pre-clinical data package and an almost complete set of clinical data, if it is considered that the remaining data will be collected in a short timeframe. To qualify, a product must be intended for treatment, prevention or diagnosis of a seriously debilitating or life-threatening disease; have designated 'orphan' status (meaning that it is intended to treat rare or ultra-rare disease); or be intended for use in emergency situations, responding to European Community or WHO recognised unmet medical needs, and immediate availability is likely to outweigh risks. Conditional Marketing Authorisations (MAs) must be renewed annually. It is notable that 10%-20% of all drug approvals are now conditional MAs, including in oncology about two approvals per annum since the mid-2000s.

Second, *Exceptional Circumstances Licensing* is available when comprehensive data could never be provided, for example because the disease is too rare, the scientific knowledge is too limited, or because of ethical issues such as constraint on submitting seriously ill patients to extensive tests. Third, *Accelerated Assessment* is designed to meet the expectations of patients and to take account of the increasingly rapid progress of science and new therapies. It applies to medicinal products supported by major interest from public health and therapeutic innovation perspectives. Application for an accelerated assessment procedure must justify itself on these grounds. The European Medicine Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) makes a decision based on the justifications presented and recommendations of independent rapporteurs. These early access pathways are not mutually exclusive. (The above two paragraphs draw on Mittra et al, 2014 and EMA, 2016).

These flexibilities are now being recast in terms of a movement toward so-called adaptive approaches. In March 2014 the EMA launched an adaptive licensing programme, inviting companies to participate in a pilot project (Ranson & Cline 2014). However, in 2013 the European Commission had stated that it was 'not

convinced' that adaptive licensing was the best way forward (cited in Ranson & Cline, 2014). The European Commission's IMI initiative (see above) is currently attempting to consolidate these and other apparent regulatory easings under the umbrella concept of MAPPS (Medicines Adaptive Pathways to Patients). EMA's Senior Medical Officer Eichler has preferred the term 'adaptive pathways', indicating a less legalistic and softer, provisional (conceptually hybrid, see Table 1) approach to flexible gatekeeping that arguably lessens the financial risk for producers (Eichler, 2015). EMA's intended adaptive pathways initiative amounts to an umbrella policy approach that would integrate a number of elements, especially related to non-conventional data requirements, such as adaptive clinical trial design, patient centric benefit/risk assessments and the continuous evaluation of a therapy as new evidence 'including real world evidence' (meaning from patient registries or patient cohort studies without control groups) becomes available. Interestingly in the context of debate about the role of consumer/patient demand for therapies, the initiative includes an acknowledgment of patient access issues as part of a life cycle approach to the innovation process. The 'expected impact' would be:

a comprehensive plan of development and exploitation of tools, methodologies, infrastructures that will allow changes in R&D, regulatory and medical practice to enable early patient access to innovative prevention and treatment options (IMI, 2014)

In the UK case, a research report following on from the House of Lords' recommendations (HoL, 2013) examined such perceived requirements to facilitate commercialisation, funding and reimbursement (Omidvar et al, 2014). Similar issues of access and methodology are being debated elsewhere in the context of RM commercialization. For example, in Canada at a recent 'Business of Regenerative Medicine course', in Toronto, in July 2014 reimbursement and accelerated approval were debated

There was particular excitement around accelerated approval regulatory pathways that are being developed to facilitate the commercialization of live cell technologies. As (a CEO of a company) put it, we're experiencing a "magical era of accelerated approval." But he also wonders about the fate of cell therapy technologies upon approval, and what is being done to link accelerated approval with reimbursement. (Curtis, 2014)

(The latter point about reimbursement is discussed further in the section on 'Gatekeeping clinical and healthcare adoption' below). Alongside pharmaceutical exceptionalism must be set certain exemptions from the dominant centralised European market entry gatekeeping that have been introduced in the 2007 ATMP Regulation. On November 13th, 2007, the European Union adopted a *lex specialis* on medicinal products based on genes, cells and tissues: Regulation (EC) No 1394/2007 on advanced therapy medicinal products (the 'ATMP Regulation'). This was a new category of medicinal product established by the law, which covers many, though not all products deemed to be regenerative medicine products. The Regulation applies to products either 'prepared industrially' or 'manufactured by a method involving an industrial

process'. This definition implied that some therapies would be deemed to be produced non-industrially, and thus a so-called 'hospital exemption' was constituted, which means that medicinal products not falling under centralised EU regulation by EU law would not benefit from a harmonized regime across the European Union marketplace, though they have to respect national laws (Mahalatchimy et al, 2012)

The ATMP Regulation institutes provision for a central and unique marketing authorization at the European Medicines Agency (EMA) level where a new Committee for Advanced Therapy (CAT) was created, meaning that once authorized, products may be made available throughout the EU member states. Four types of biological medicinal products were defined as ATMPs: gene therapy medicinal products (GTMP), somatic cell therapy medicinal products (CTMP), tissue engineered products (TEPs) and combined ATMPs which combine a medical device (legal category) with an advanced therapy. This is therefore the dominant gatekeeping paradigm for regenerative medicinal products in the European Union.

The EMA through the Committee for Advanced Therapies can provide an informal scientific recommendation on the classification of products, and this has emerged as one its primary activities. Unsurprisingly, there are difficulties in distinguishing products which are covered and products which are not by the definition of industrial process. The European Commission has tried to clarify it as follows:

This should cover, inter alia: Any "mass production" of advanced therapy products for allogeneic use (batch production, "off the shelf" products etc.); any advanced therapy product for autologous use (i.e. using cells/tissues from a single patient and re-implanting after manipulation) which, although being patient-specific by definition, is manufactured in accordance with a standardised and industrial process.

This distinction is crucial to defining the status and responsibilities of producers of regenerative products, whether in hospitals or in the commercial sector. Thus the Hospital Exemption has emerged as an alternative, national-level gateway to clinical application, and is one of the most controversial features of the Regulation and its implementation in different EU member states. In fact, the proposal of this measure was controversial from the start. An internal EU document noted the differing views about the new principle:

products prepared in a pharmaceutical enterprise not under this exemption would require clinical trials...but similar products prepared for the same use under the exemption (i.e. in a hospital for a single patient) would not (Council of European Union, 2007)

The shift in the Commission strategy toward advanced therapies thus brought with it a shift to a new principle in which the mode and locus of production has become dominant. The new organising principle rests on matters in particular of the *scale* of activity and the *industrial, repetitive or nonroutine* nature of the enterprise. Here we see a central gatekeeping attempt to define a borderline between capitalist

commodity market and non-market forms of the technical practice of tissue and cell therapy, typically, though not straightforwardly, institutionalised in the distinction between hospitals and commercial enterprises (and leaving aside such difficult issues as the fact that there is no legal definition of a hospital in EU law, and that the legal entities which constitute healthcare providers vary greatly across the EU). However, it should be noted that the Hospital Exemption has only been given to one manufacturing site in the UK at the time of writing, possibly because most clinical applications to date involve transport of materials across national borders, which is not allowed under that scheme – unlike an alternative gateway, the so-called ‘Specials’ scheme (see below).

In UK law, the MHRA has provided guidance on what constitutes non-routine preparation of a product (MHRA, 2010). Two main areas are taken into account: First, is it the same product repeatedly under consideration? Second, what is the scale and the frequency of the preparation of the specific product? The MHRA has also developed guidance on the UK’s arrangements under the hospital exemption scheme (MHRA, 2010). This sets up specific standards as regards good manufacturing practice (GMP) and quality, pharmacovigilance, traceability, reporting requirements, sanctions and penalties, requirements in respect of wholesale dealers, and requirements not specified within the Regulation but which will apply under the exemption in the UK such as labelling, package leaflet requirements and advertising (Mahalatchimy et al 2012).

It is known that different member states in the EU interpret and apply the hospital exemption in different ways and are creating different criteria to define industrial and repetitive production. It has also become clear that some developers/producers see this as an attractive option, and the EMA has expressed concern that the exemption not be over-used in terms of numbers of individual patient applications -thus distorting the marketplace for commercialised products - nor that member states fail to apply analogous safety criteria to the production processes and resulting therapies. EMA’s concern also includes both market distortion and the safety specifically regarding stem cell products (EMA, 2010).

Alongside the hospital exemption, the UK had previously created a pharmaceuticals ‘Specials’ scheme under 2001 European Union pharmaceuticals legislation which provides: ‘A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this (medicines) Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility’. For such products, no product licence or marketing authorisation is required, but a manufacturer’s (Good Manufacturing Practice -GMP standards) licence is required. Under this scheme, doctors and certain other prescribers can commission an unlicensed relevant medicinal product to meet the special needs of individual patients. (Mahalatchimy et al, 2012). The MHRA does not publish the names of products regulated as Specials or under ATMP hospital exemption; in

contrast, in Germany to give one example, it is reported that a personalised immune therapy for certain brain cancers, DCVax-L ® produced by U.S company Northwest Bio, has been approved under hospital exemption; this product, coincidentally, was also the first product to be given a ‘Promising Innovative Medicine’ designation by the MHRA in the UK (see section below on ‘Gatekeeping clinical and healthcare adoption’).

The role of the Committee for Advanced Therapies (CAT) continues to evolve, partly in interaction with other perceived stakeholders. For example, in a summary of its work programme from 2010, its Chair mentioned its role as including: ‘a joint conference on ATMPs involving EMA/CAT, EFPIA, EBE, EUROPABIO (the latter three are trade associations) (and) Learned Societies to share clinical, scientific and regulatory expertise in the field for the benefit of all stakeholders’ (Schneider 2014; author was Chair of CAT). This statement was presented at an EMA conference on regulatory science ‘Regulatory science: are regulators leaders or followers?’ in 2010. Gatekeepers also appear willing to explore innovations in regulatory science that would enable good quality in vitro data to play a greater role in early stage proof of concept and safety (Mittra et al, 2015). Other CAT initiatives were to consider whether to: ‘Extend incentives for SMEs to academia, hospitals, trusts and small research groups?’; and to “Promote access and availability for patients’: ‘Consult (with national regulators) on hospital exemption’; ‘Encourage development of ATMPs for unmet medical needs without alternative treatments’. The performance of the ATMP Regulation was subjected to public consultation during 2014, and these issues figured prominently in critical comments submitted (European Commission Health and Consumers Directorate-General, 2015). Criticism of the hospital exemption, insufficient adaptation to particular characteristics of regenerative products, and the lack of special incentives for academia and hospitals, emerged especially strongly from this public stakeholder consultation.

Another alternative to the dominant obligatory passage point or gateway of centralised pharmaceutical/ATMP gatekeeping is, arguably, designation of a new cell technology as a medical device. This is seen by some developers as a less stringent route in Europe for RM products, compared to the pharmaceutical route. In the EU medical device market assessment is made by devolved ‘notified bodies’ which are specialist technical centres with particular expertise in different types of devices. Products are given a classification according to the deemed level of physical health risk. This can be a realistic and crucial consideration for developers, because the ‘primary mode of action’ of given technologies is by no means always clear-cut, and indeed is one of the aspects that regulators such as the Committee for Advanced Therapies regularly adjudicates on. Thus for example the rise of ‘closed system’ centrifuge technologies in which a patient’s cells are processed within a single operative procedure to isolate ‘regenerative cells’ (for example, producers Cytori; Regeneus), which may include adult/mesenchymal stem cells, are regulated as medical devices.

So there are a range of political developments in the gatekeeping regime designed to allow potentially beneficial innovative technologies to be used to a greater or lesser degree, under various conditions, in some cases prior to full marketing authorisation. As has been noted, some of these are mandated within legal/regulatory frameworks, whilst others are not. The regulatory policy initiatives are summarised in Table 1's left-hand and middle columns. These political developments evident in the policy discourse that I have analysed introduce and apply alternative gateways that make the overall gatekeeping regime more flexible for participating actors. Their 'adaptive' nature can usefully be understood as a means of maintaining connection between the gatekeeping regime and the ever-evolving and regulation-challenging technoscientific field in question.

<Table 1 about here>

Gatekeeping clinical and healthcare adoption

In this section, I consider the policy discourse and activity of recent discussions and developments in the MHRA, NICE (National Institute for Health and Care Excellence) and NHS England, the National Assembly for Wales, and high-level Regenerative Medicine Expert Group meetings during 2014 (in which the author participated), which was formed on the recommendation of a 2013 House of Lords Science & Technology Committee report on RM. The *modus operandi* of the MHRA has been noted above (introduction to 'Gatekeeping the market' section); NICE is England and Wales' national central health technology assessment agency, evaluating and making decisions about the acceptability of new drugs and devices for the public National Health Service, in the context of existing technologies and standards of care. It produces legally mandated Technology Appraisals based on extremely detailed quantitative and statistical re-evaluations of all relevant studies of clinical and cost-effectiveness of particular technologies and a wide variety of other recommendations, guidance and clinical guidelines on specific medical conditions and health service areas. This work is undertaken through a variety of multidisciplinary expert committees, its own technology assessment staff, and contracted-out technical assessment agencies. It largely applies a utilitarian philosophy of maximum benefit to the population, hence the principles of health economics in making technology assessment decisions using the QALY methodology (see below) are to the fore.

NHS England (NHSE) is the purchaser of national level Specialised Services (for example for some cancers) where national-level planning is deemed necessary, and negotiates policies in particular medical service areas which are then 'commissioned' by regional bodies (currently called Clinical Commissioning Groups). It is charged with implementing the results of NICE's Technology Appraisals. NHSE conducts some its own technology assessments collecting and reviewing available clinical study evidence, where NICE has not done

so, and operates with advice from expert clinical specialists arranged in Clinical Reference Groups. Again, I focus on the apparently relaxative exceptions and exemptions that appear as alternative gateways being created in and around the dominant obligatory passage points of gatekeeping associated with the structures, organising categories and methodologies of these institutions, and the contested positions, interests and methodologies around them.

In the UK, one of the schemes now being embraced under the MAPPS (Medicines Adaptive Pathways to Patients) concept referred to above is the 'Early Access to Medicines Scheme' (EAMS) (MHRA 2014), which was instigated in the government's 2011 new *Strategy for Life Sciences*. This scheme 'aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need'. Subsequently, a new special designation has been created for promising products: 'Promising Innovative Medicine' (PIM). A PIM designation, awarded by the MHRA, is a necessary first step in, and increases the likelihood of a company being able to achieve a positive scientific opinion for formal Early Access status for its product, thus making it available, pre-licensing, to patients. Regenerative medicine products are within the scope of the scheme: as the MHRA website proclaimed in November 2014: 'MHRA awarded the first PIM designation for a cell therapy product for the treatment of cancer on 8 September 2014.' (The treatment is for glioblastoma, but the names of the product and company are not in the public domain). PIM designation refers to:

Promising Innovative Medicine' and 'will give an indication that a product may be eligible for the Early Access to Medicines Scheme (based on early clinical data). The PIM designation will be issued after an MHRA scientific meeting and could be given several years before the product is licensed (MHRA 2014).

The scheme is distinct from the adaptive licensing discussed above which operates *within* existing market authorisation law, and mandates the producer to provide the therapy outside the marketplace, *at no cost* until licensing is achieved. The scheme has been supported by the British government in consultation with trade associations and other interested parties during 2014, in response to earlier stakeholder consultations by MHRA and the Department of Health (UK Government, 2014). The scheme explicitly addresses 'the landscape for early access to medicines which reflects the UK Life Sciences Strategy and NHS Innovation Health and Wealth reforms', and 'Reflects the profound changes driven by Genomics, Data, and the rise of Stratified and Personalised Medicines' (ibid, p3). Notably also, patient group involvement is explicitly recognised in the early adoption process: 'Encourages startups, patient groups and charities to collaborate within the extensive infrastructure via the National Institute for Health Research (NIHR) funded Clinical Research Facilities and Biomedical Research Centres and Units in leading NHS Trust/university partnerships'. The government response also mandates for 'a newly coordinated NICE technology appraisal and NHS England Commissioning process'.

The first product to be accorded full EAM status within the legal framework was announced in early 2015: Pembrolizumab, a monoclonal antibody produced by US company Merck: ‘a positive scientific opinion has been awarded for a medicine used to treat advanced melanoma’ (MHRA CEO Hudson, March 2015). While not a regenerative medicine itself, this development nevertheless strengthens the viability of this alternative gateway, to which a PIM-designated product may be promoted. The data requirements for the EAMS scheme are less onerous than the full marketing authorisation application dossier which would otherwise be required: ‘The trigger for an Early Access to Medicines scientific opinion does not necessarily have to be the submission of a dossier for marketing authorisation application, but the availability of a sufficiently compelling case based on the total data and evidence collected to date as assessed by the MHRA’ (MHRA, 2014). While the Early Access Scheme is operated by the market-entry gatekeeper the MHRA, it requires coordination with NICE and NHS England as the commissioner of health services, including especially NHSE’s Specialised Services (NHSE, 2012). NHSE’s Specialised Services strategy is to have a ‘clear focus on a range of rare conditions and low volume treatments ranging from medical genetics, kidney disorders and uncommon cancers to complex cardiac interventions, burn care and some specialised services for children’ (NHSE, 2012). The rationale for this set of services is thus to provide services for relatively rare medical conditions with severe effects, and may thus apply to regenerative products.

The potential for tensions and potential non-alignment between the two forms of gatekeeping that I have been discussing here (noted also in the section above) is high. There are examples of market-authorized products with regenerative claims, which have not been authorised by national HTA bodies such as NICE in the UK. Short of HTA negative opinions, there are examples of national HTA processes resulting in requests to a manufacturer of a cell therapy product to undertake more research to address particular information deficits. An example of this decisional route from NICE is ReCell TM a spray-form product for burn injuries: ‘The medical technology guidance on the ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury recommends further research. This recommendation is not intended to preclude the use of the technology in the NHS but to identify further evidence.’ (NICE, 2014). Such policy positions clearly attempt to steer a course between commercial interests, clinician decision-making, and national system-level evidence appraisal.

NICE was strongly represented in a Regenerative Medicine Expert Group (RMEG) during 2014, constituted to advise the British government on policy to support RM as a sector following the Life Science Strategy and the House of Lords report referred to above (HoL, 2013). RMEG membership has been composed of a wide range of stakeholders including big pharma, SMEs, clinicians, NICE and NHS England policy staff, private health insurers, charitable funders, disease-based patient representative organisations, and social scientists. Its work was arranged into three groups, focused on Delivery, Regulation & Licensing, and Evaluation & Commissioning (a NICE official was made Chair of the latter group). One recommendation was

to create a high level Ministerial Strategy Group for regenerative medicine (paralleling existing groups for medical technology and pharmaceuticals), however, this proposal was rejected by the Minister for Health.

The overall tenor of the RMEG discussions about technology appraisal of regenerative medicines was that the existing methodology (including QALYs,¹ clinical evidence and cost effectiveness analysis, etc.) was adequate and was already applied successfully to other innovative medicines. However, the following potentially concessionary proposal was agreed, stated to be initiated by NICE and endorsed by RMEG :

to undertake one or two 'mock' technology appraisal studies, on exemplar regenerative medicine products. Such studies could include T cell therapies where there are a number of products in development. (RMEG Report, 2015)

Alongside NICE, as national commissioner of health services NHS England undertakes some technology assessments that NICE does not undertake, and contracts with providers in order to secure services for the population, including the aforementioned Specialised Services. Alternative payment or reimbursement schemes for innovative technologies were also widely debated. The RMEG report discussed pros and cons of 'risk-sharing' schemes between NHSE and local commissioners and commercial technology providers (payments related to ongoing patient outcomes evaluation), noting their drawbacks, and refers more positively to NHSE's recent 'Commissioning through Evaluation' (CtE) scheme, which is applied to a limited number of therapies, and which enables HTA assessment to be undertaken while a technology is introduced in a limited number of sites. The RMEG concludes on this issue with a very general, flexible recommendation, simply that 'an innovative business model' should be developed (RMEG, 2015).

NHSE had set up a working group on regenerative medicine in response to the House of Lords report. The following recommendation also is made in the RMEG report, to strengthen this cross-cutting initiative:

the cross CRG (Clinical Reference Group) working group for regenerative medicine set up by NHS England to support RMEG should be further developed into a formal 'CRG for regenerative medicine'. It should include clinicians covering a wide range of specialisms and experience in regenerative medicine to provide specific insight and advice on regenerative medicine products to other CRGs and NHS England. (RMEG, 2015)

Another possible relaxation is 'value-based assessment' (VbA). This is a methodological HTA/NICE development which arguably extends the possibilities for RM products becoming adopted in the NHS, especially because many of these products promise long-term benefits, that may not easily be captured by existing methodologies. The VbA concept had been partially developed by NICE following extensive

¹ QALY = Quality-adjusted Life Year, 'A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score.' (NICE definition)

consultation, highlighting a high degree of uncertainty around the definition of the concept. It is currently unclear if or how this will be incorporated into NICE's assessment methodologies and organisational infrastructure, and how closely it would be tied to, or equated to, the QALY methodology (NICE, 2014). In a former incarnation, the intention was to develop value-based *pricing*, whose three dimensions identified for methodological development were: 'burden of illness', 'therapeutic improvement' and 'wider societal benefits':

...we intend to consider the wider impact of a disease on people's ability to be part of society. We refer to this as the 'wider societal impact' and define it as the loss (or shortfall) in a person's capacity to engage with society as a result of living with the disease or condition, compared with their capacity to engage with society without the condition. We propose calculating wider societal impact by measuring the absolute shortfall in QALYs (NICE Consultation, 2014: 7)

The tension between existing methodology and the new proposals is evident here (in the proposal to retain the QALY method as the basis for wider societal impact assessment rather than population health status and longevity). Attempting to reinforce the extension of QALYs, later in the document we see: 'Since loss of good health affects a person's ability to engage in society, societal shortfall can be assessed by measuring the absolute QALY loss' (p11). Nevertheless, if this methodological innovation were to be implemented, it would imply a widening of the goal-posts or oiling of the hinges of the gateway controlling products' entry into the UK healthcare marketplace, by extending the criteria of assessment. In principle VbA thus means that a broader, social-good oriented approach to valuing technologies could be used, an example, crudely speaking, being the inclusion in gatekeeping evaluations of potential knock-on effects of a technology on return-to-work of previously incapacitated patients, with its consequent calculable impact on the economy. However, the development of VbA stalled on this point, partly under criticism that it would operate in an ageist way, favouring for example formal economic activity over informal, less calculable caring.

A further exceptional gateway by which novel technologies that have been approved for the marketplace but not for national commissioning is the Individual (Patient) Funding Request, which is available to individual clinicians in cases of exceptional need (IFRs in NHS England; IPFRs in NHS Wales). This is a further route that has recently attracted policy attention in the UK. NHS England has introduced a requirement that should five such requests be received for the identical therapy, then a national policy should be created for commissioning the technology as part of a clinical service at one or more provider centre. The Welsh government recently reviewed the implementation of this practice too, resulting in a new, more coordinated policy. The system will apply to the so-called orphan and ultra-orphan medicines and treatments for patients with rare diseases (Welsh Government, 2014), a designation that many developers of RM products are known to be seeking.

Thus, as with 'Gatekeeping the marketplace', a range of apparent easings and potential easings in the form of alternative gateways to the dominant centralised regimes, appear to be being introduced in gatekeeping of healthcare adoption processes and systems too. These are summarised in Table 1's right-hand and middle columns. In the same way, these innovations in the healthcare gatekeeping regime represent systemic adaptations to the pressures produced by innovative regenerative medicine products and their proponents. The political adaptations in the gatekeeping regime should be seen as attempts by policy actors to maintain what I have termed gatekeeping connection between the institutions and epistemic cultures of the healthcare system, and the challenges produced by the innovating technoscientific field.

Discussion

Reviewing the developments outlined above, we note that not all the regulatory easing and gateway construction that we witness is specific to regenerative medicine or cell therapy, although as I have pointed out there are some developments distinctive to the RM sector. Table 1. summarises in its middle column the range of 'hybrid' alternative gateway schemes that I have described, and which are proliferating, being designed to overlap the market authorisation on the one hand, and healthcare assessment and adoption gatekeeping arenas on the other. As one would expect in the case of technoscientific developments of high uncertainty and high promise, the volume of political debate and conflicting interests in the regenerative medicine field is massive as this paper illustrates. The actors and institutions erecting and organising the gatekeeping regimes could have maintained stricter, more centralised, less flexible forms, so it is clear that some conditional concessions and participative approaches between stakeholders have become part of the gatekeeping system.

The forms that the regenerative medicine policy and debate takes includes not only the mushrooming of working groups and conflicting interest group forums around the legal/regulatory issues, but also the tension at least in the UK between an attempt to align regenerative medicine's market gatekeeping with the existing HTA-based regime focused nationally around NICE on the one hand, and the proliferation of policy-oriented multi-stakeholder working groups such as the Regenerative Medicine Expert Group on the other. There are escalating calls for increasing dialogue between market regulators and HTA actors such as NICE and payers such as NHS England more widely in regenerative medicine stakeholder communities. In the UK, there are currently moves to create closer coordination between NICE and the MHRA and between NICE and NHS England. Such links between the two gatekeeping arenas that I have discussed above may be increasing more in some jurisdictions than others. In fact the EMA since 2010 has offered parallel scientific advice with HTA bodies to attempt to allow medicine developers to establish the required evidence base, in a process sometimes termed 'parallel review'. A draft best practice guidance for EMA-HTA parallel scientific advice was published for public consultation in May 2014 (EMA, 2014), and we can note that a form of 'parallel review' was adopted by Health Canada and the Canadian Agency for Drugs and

Technologies in Health for all new drugs in late 2012. These developments closing the gaps between the gatekeeping regimes of the regulatory and healthcare system adoption domains can be seen as ‘hybrid’ forms gatekeeping, as shown in the middle column of Table 1.

The importance of this tension seen in cases of disjunction between market authorisation gatekeeping and healthcare adoption gatekeeping, can instructively be compared to cognate developments in other parts of the world. In South Korea for example, a country that has been progressive with approval of regenerative medicine products, regulators had approved 16 therapies to 2014 – said to be the most of any country in the world – but apparently technology assessment and payment systems as part of the healthcare gatekeeping regime have not supported these same technologies through reimbursement decisions. Not one has been reimbursed or exported out of the country (Curtis, 2014). On the other hand, a precedent in attempts to ease this alignment and reduce the tension can now be found with Japan’s recent regulatory innovation, where the government has implemented a conditional approval system. Cell therapy developers are now only required to have a single, albeit larger, Phase 1 study to achieve marketing approval. (Interestingly, all the cell therapies currently approved in Japan, though small in number, are entitled to reimbursement, a converse of South Korea).

In considering the fundamental tension between market access and healthcare adoption gatekeeping, we can note that adaptive licensing and the early access scheme in the UK, although legally and conceptually distinct in addressing licensing on the one hand, and adoption/access on the other, do align with each other in attempting to achieve conditional forms of availability of innovative medicines in the two gatekeeping regimes. In a more global perspective, the analysis presented in this paper can usefully be set alongside analysis of cell therapy and other regenerative medicine gatekeeping developments in other parts of the world, which focus on inter-national variations and connections (Sleeboom-Faulkner, 2013), in order to further our understanding of competition in the global bioeconomy and collaborations that are interlacing through it.

It is of interest to question the origins and forces influencing the proliferation of the novel, hybrid, flexible gatekeeping regimes reported here. Most obviously perhaps, does a political analysis pointing to the influence of the pharmaceutical industry hold water in explaining these trends? More specifically, does the long-established and ongoing analysis of regulatory capture (for example, Carpenter and Moss, 2014) provide a reasonable account of these developments? Although this paper has set out to describe gatekeeping modifications and their potential impacts, rather than the forces at work in their construction, some speculative, though inconclusive, remarks are in order. As noted by Ehman et al (2013) cited in the introduction to this paper, regulators themselves acknowledge that their institutions and practices undertake not only gatekeeping roles but ‘facilitating’ roles vis-a-vis manufacturers and producers of new medical products. However, in the case of regenerative medicine, the participation of the multinational

pharmaceutical companies is in a very embryonic stage, and most of the activity lies with academic hospitals and small companies.

Of course it is always the case that an industry would like harmonised regulation across different geographical jurisdictions such as the European Union and a 'level playing field' of regulatory demands with other innovators. In the UK, given the increasing calls for, and actions implementing, closer coordination between gatekeeping of market entry and gatekeeping of healthcare adoption and payment, the interests of manufacturers are encountering the forces of health technology assessment and cost effectiveness-based planning ever more closely. Thus, while there is demonstrable proliferation of alternative gateways, these are limited in the access that they give to potential markets, and the mandated and legitimate power of HTA institutions such as NICE, with their deep commitment to utilitarian population health values, leads to a very constrained suite of apparent relaxative gateways, conditioned by constant re-appraisal of emerging clinical outcomes, formal evaluation of evidence, and potential withdrawal of conditional authorisations and reversal of conditional payment schemes. The extreme uncertainty of clinical outcomes for patient groups in many regenerative medicine developments doubtless underlies this picture of diversification and experimentalism in the gatekeeping regimes, rather than matching a template of regulatory capture.

In a similar vein, the influence of patient organisations should be considered. It is certainly notable that many of the regenerative medicine products currently under development or in the marketplace concern rare diseases, and many of these have or seek 'orphan' status, which, while indicating relatively small potential patient populations clearly are seen to represent a business model for some companies which can offer a novel product for unmet needs at a viable, high price. Orphan status brings with it various fee waivers in the market regulation process and, if a marketed product finally results, gives the manufacturer a ten-year monopoly over its production (Hyry et al, 2015). Although a discourse of 'early access for patients' has become routine in the gatekeeping policy networks described here, this cannot be dismissed as purely rhetorical. As noted above for example, in the case of the UK's implementation of the Early Access to Medicines scheme, patient involvement is explicitly promoted in this initiative. While it is impossible to clearly disentangle the respective influence of different stakeholders here, it is clear that patients' interests, either directly or indirectly through advocates, is having some role in *selectively* shaping the direction of regenerative medicine gatekeeping developments.

Conclusion

This analysis has addressed the question of the extent to which and forms in which there are emerging flexibilities in existing and developing gatekeeping regimes applicable to regenerative medicine, and the extent to which such flexibilities might promote regenerative medicine products as a sector, in the UK and EU contexts. I have developed the family of concepts of gatekeeping regimes and gateways from those of

regulatory regimes and regulatory connection in order to analyse how both regulatory and healthcare adoption policies taken together are being flexibly adapted to maintain what I have termed 'gatekeeping connection' with a high-profile emerging biomedical sector. In this nascent sector where conflicting interest dynamics are prominent, there is clear pressure to accelerate acceptance of products, seen in moves to overlap the domains of market regulation, health technology assessment and healthcare system planning in the hybrid gateways that I have analysed (Table 1).

Should the flexibilities of special treatment being afforded to regenerative medicine that are considered in this paper be seen as fruitless gatekeeping after the cattle have already broken down the fences? In other words, are there now so many flexible exceptions and exemptions or alternative gateways being constructed around the dominant gatekeeping institutions and methodologies that the small but swelling tide of novel RM technologies is unstoppable and irreversible? I conclude that this is not the case. The extent of proliferation of flexibilities can too easily lead to an over-estimation of their significance. Although, as this paper shows, there are a number of diversifying, hybrid easings and relaxations of the prevailing centralist regimes (summarised in Table 1), and various exceptions and exemptions, their scope is somewhat limited, in spite of the few examples of early conditional authorisation and the like. And as noted, accelerated approval systems may not actually result in incentivisation and faster approval times (Boon et al, 2010) or more efficacious products (Davis and Abraham, 2013). This limited scope of exceptions and exemptions to dominant central regimes is defined by narrow criteria of rare disease, 'orphan' designation, critical but selective disease applications such as cancer, non-routine and thus restricted production runs, emergency or unmet need, and individual medical prescription.

Returning, finally, to the conceptual developments explored in this paper. Considering the notions of 'regulatory connection' (Brownsword, 2008) and commensuration with existing gatekeeping regimes, aired in the introduction, I developed a family of concepts of 'gatekeeping', 'gatekeeping regimes' and 'gateways' as an apparatus that can help understand both market regulation and healthcare adoption passage-points with a single conceptual vocabulary, which is a novel approach and which enables an over-arching conceptualisation of the empirical trend of convergence of flexibilities into the hybrid forms that I have described. It is clear from my analysis that there is a 'politics' of gatekeeping connection and development of adoption gateways in the context of existing regimes, in which stakeholder interests interact and compete in various ways, at various levels and in different institutional sites. The apparent adjustments, relaxations and resistances, and construction of alternate gateways in the gatekeeping regimes that I have reviewed, which appear to make obligatory passage points somewhat less universally obligatory in practice, show a complicated, mixed picture of the actual and potential emergence of regenerative medicine in face of existing institutional regimes, epistemologies and methodologies. The maintenance of gatekeeping connection is being developed through both resistances and relaxations, as a range of alternative gateways to the marketplace and to healthcare adoption appear, slowly and hesitantly, to be proliferating¹. Given

this trend, further research should track the future directions and forms of gatekeeping regimes and gatekeeping connections that may develop, not least in the UK context of Britain's impending departure from the European Union. Likewise, the effects of the gatekeeping regime's exceptions and conditional contracts on producers' innovation pathways, approved and adopted product volumes, and populations' health impact require systematic evaluation.

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Table 1. Dominant and flexible gatekeeping regimes

Dominant gatekeeping regimes: Strict, Central, Legal	EU Pharmaceutical directives ATMP/EMA-CAT Centralised; UK MHRA implementation and guidance; National Health Technology Assessment/NICE		
Flexible gateways Exceptions & exemptions: Less strict; multiple; alternative	Legal/market regulatory gateways ATMP Hospital Exemption Adaptive licensing ‘Specials’ license (UK only) Orphan designation Exceptional Circumstances Accelerated Assessment Medical device	Hybrid gatekeeping: legal easing; broadening criteria Early Access to Medicines Scheme (EAMS)/Promising Innovative Medicine (PIM) designation Adaptive pathways (MAPPS) Conditional approval Value-based assessment (if implemented)	Adoption gateways Commissioning through Evaluation NHS Executive specialised schemes Risk-sharing Multiple individual patient funding requests

ⁱ A current REGenableMED project (<https://www.york.ac.uk/satsu/regenablemed/>) aims to analyse these dynamics in detail in the UK case to assess business models and the readiness of the UK health system for regenerative medicine as an economic, biomedical and healthcare enterprise.